



In Silico Studies of the ToxCast Chemicals Interacting with Biomolecular Targets

M.-R. Goldsmith^{1,2}, S. B. Little¹, D. M. Reif¹, K. A. Houck¹, D. J. Dix¹, T. R. Transue³, A. V. Singh³, T.B.Knudsen¹, J. R. Rabinowitz¹

1 National Center for Computational Toxicology, Office of Research and Development, U.S. EPA, RTP, NC;

2 National Exposure Research Laboratory, HEASD-EDRB, Office of Research and Development, U.S. EPA, RTP, NC;

3 Lockheed-Martin, RTP NC, USA

research & development

Abstract & Background Information

Molecular docking, a structure-based *in silico* tool for chemical library screening in drug discovery, can be used to explore the interaction potential of environmental chemicals acting at specific biomolecular targets. In this approach, an approximation of the free energy, $\Delta G_{\text{complex}}$, of the formation of the complex between the environmental chemical and target is obtained. The results correspond to the equilibrium binding affinity, K_{d} , of a chemical with a target. By docking many ligands into many targets, a **Virtual Affinity Fingerprint Matrix (vAFM)** is constructed and the structure/ multi-target affinity signatures explored.

The exhaustive docking algorithm in the eHTS programs (SimBioSys Inc., Toronto, Ontario) was applied to construct a vAFM of a diverse set of environmental chemicals docked to 18 nuclear receptor (NR) crystal structures (PPAR- α/β , ER- α/β , PGR, AR, MR, LXRxR, PXR, CAR, RTR, FXR, GR, MR, ROR α , RXR α). The data was clustered in chemical/target space and specific clusters were profiled. A molecular basis for differentiating promiscuous, tight-binding ligands from non-binding and selective ligands was developed and the findings were corroborated with current NR literature.

With the same approach, a vAFM of several thousand chemicals containing known endogenous ligands, therapeutic compounds and 306 ToxCast chemicals is being developed for ~150 ToxCast targets, including NRs, kinases, phosphatases, CYPs and esterases. These *in silico* results will be coupled with ToxCast *in vitro* assay data and *in vivo* endpoints to provide mechanistic insights, and to determine a practical strategy for using molecular docking results in a screen for chemical toxicity. [This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.]

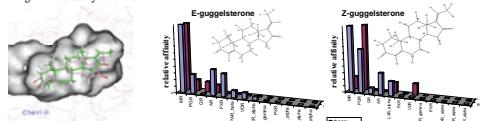
Method: Docking of chemicals into Receptors

Provided with the 3D conformation or structure of both a target (biomolecular receptor) and a putative toxicant (ligand) we wish to evaluate 3 primary molecular level questions: (1) Does the molecule bind? (i.e. the ligand complementary to the receptor) (2) How strong is this binding affinity? (or ligand / receptor) (3) What does the toxicant / target (or ligand / receptor) complex look like? The docking method used in this study is an efficient and computationally scalable divide-and-conquer approach, using a trainable empirical scoring function as implemented in eHTS 6.1. A schematic representation of the method is illustrated in the figure to the left (Zsoldos 2006, ibid).

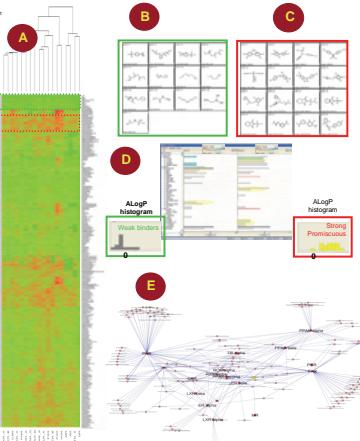
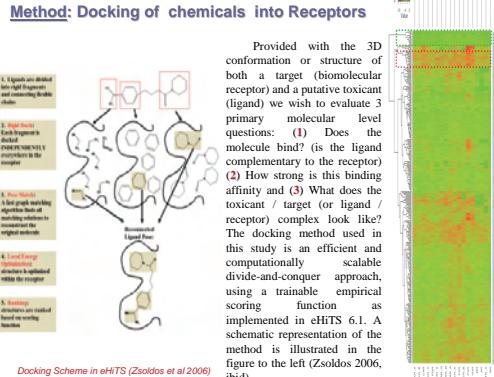
Docking Knowledge in eHTS (Zsoldos et al 2006)

Validation: Virtual Screening for Target Elucidation of Ligands : Multiple-target binding of Guggelsterone isomers

We docked two known multiple-nuclear receptor binding natural product ligands (E & Z-Guggelsterone) geometric isomers against multiple human NR crystal-structure targets in their agonist-associated (active) conformation (from www.pdb.org) and MMFF94 optimized ligand set geometries with AM1-BCC charges assigned from MOE (www.moe.com) as found in Kibab (Aizawa 2004) curated from the original publication on guggelsterone polypharmacology (Burris, 2005). The docking was performed in eHTS on "fast" screening mode (Zsoldos et al 2006). The structure of both isomers are shown docked within the binding pocket from MR (mineralocorticoid receptor) one of the top hits for both isomers. The structural formula is shown overlaid on experiment/theory rank ordered bar graphs (magnitude normalized binding affinity (K_{d}) to highest value = large bars = high affinity). This multi-target NR screen qualitatively and quantitatively agree with experiment, a useful tool for screening or "fishing" for putative targets and enabling *in vitro* assay selection.



Previous NR class-specific vAFM: Docking to 18 Nuclear Receptors



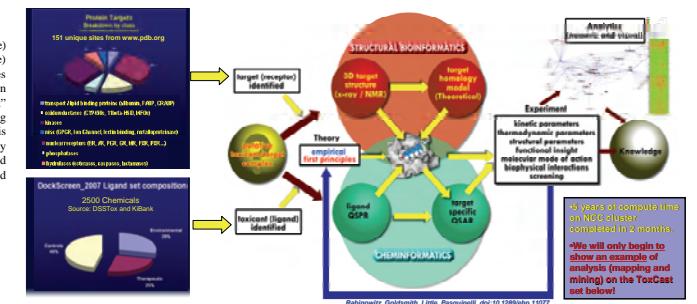
Docking of ~400 environmental chemicals against a set of nuclear receptor targets afforded us (A) a vAFM that was heat mapped / hierarchical clustered in R with two key groups outlined (B) weaker binders in green box and (C) strong NR binding promiscuous cluster in red box. (D) Both ALogP and Chemical (functional group) feature histograms generated in LeadScope for both clusters illustrating major differences in these clusters that corroborate well with current knowledge of NR ligands. (Paolini et. al. *Nature Biotechnology* 24, 805 - 815 (2006))

E) Linkage Map Analysis

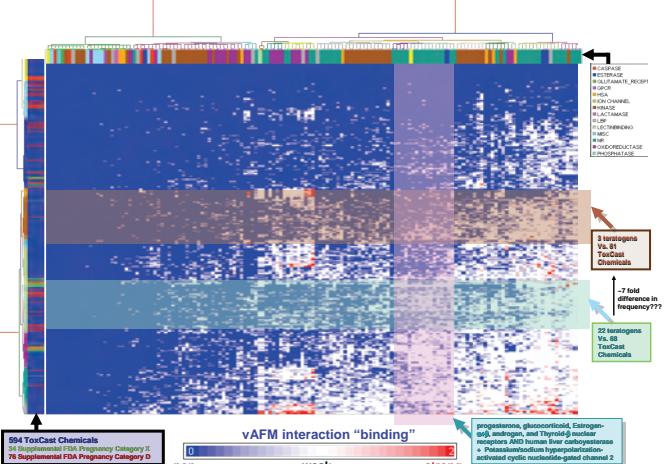
The higher affinity (i.e. top tier) chemicals from (A) that have theoretical $\log K_{\text{d}} < -6$ (~ 132 chemicals / nodes and 285 links / edges) were plotted as a linkage map in Cytoscape.

Interesting unique clusters and multi-target sets can be identified, in addition to chemical space placement of the receptors.

In Silico Workflow: Docking 2500 Chemical into 151 Diverse Targets



An example of analysis/knowledge mining of ToxCast™ Chemical Subset: 151 Target / ToxCast Chemical clustering & supplemental chemical clustering of known phenotypes



Preliminary Conclusions

• Our previous NR class-specific docking studies (red/green heatmap) demonstrated the practicality of an approach that identifies and clusters both chemicals in a given target-space, and targets in a given chemical space identifying some compounds that show both (I) high NR promiscuity and strong affinity as well as (II) high NR specificity with varying degrees of affinity (or no affinity). The top structure in this class is strikingly similar (structurally analogous) to a known multi-NR-binding environmental obesogen. The target-space clustering in the context of these ligands suggests that strong promiscuous binders have fewer polar heteroatoms, higher halide and multi-substituted biphenyl incidence, and higher LogP partitioning characteristics.

• Phase I ToxCast chemicals cluster analysis (blue/red heatmap) provides knowledge in terms of chemical similarity within target space that can be rationalized in a similar way to our previous study.

• Hydrolases, some serum sites, caspases, esterases clustered to top left (primarily blue region) consist of more polar and larger ToxCast chemicals that bind less to the entire target set.

• Most of the tight and mid binders of the ToxCast set are located in a clusters that consist of fatty-acid binding proteins, some albumin sites, many NR and oxidoreductase targets. Considering the higher LogP of these chemicals compared to random diverse chemical subsets this may be rationalized by the fact that these primarily α -helical globular protein targets consist of residues at their interface that are primarily non-polar.

• The top cluster of the cluster analysis is the kinase class, where the upper hits (above 1st horizontal bar) differ in kinase affinity compared to all lower subclusters.

• Not all of the stereoisomers of a ToxCast chemical enumerated fall within the same cluster, indicating potentially substantial stereoselective differences. Interestingly, there is an example of one pyrethroid class pesticide where multiple stereoisomers have been enumerated where all isomers do cluster together, however, key NR and CYP targets still had substantially different affinity signatures.

• These in silico data points can undergo data fusion with other types of assays (for instance *in vitro*) and supplemented with chemicals of known adverse outcome (i.e. neurotoxic, carcinogenicity, etc...) and binned accordingly to add information content for subsequent knowledge mining.

• Supplementing ToxCast Chemical *in silico* signatures with those of chemicals that elicit known adverse phenotypes enables cross-cluster comparison, and potentially phenotype elucidation. For instance, the lower row on the heatmap consists of $\sim 7 \times$ higher incidence of supplemental teratogen, FDA pregnancy category D and X) than the upper row. The key difference between these two rows is shown by a vertical column that suggests the importance of chemically non-specific binding receptors as potential disruptors for these mode. Similarly first-pass literature search for teratogenic potentials of nearby ToxCast neighbours do indicate some of these chemicals to elicit more than suspect teratogenic/reproductive potential, although further studies to corroborate such analyses with other assay endpoints and the DevTox initiative of the NCCT and ToxCast are still underway.

• Means to more efficiently identify and enumerate biologically/environmentally relevant permutations and progeny of the parent chemical structures in question would be highly desirable, however these vHTS studies of parent compounds already provide valuable molecular-level detail in the toxicant-target paradigm that are complementary to hypothesis-driven *in-vitro* HTS and toxicogenomic inquiry.

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